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## Letter to the Editor

## High vaccination coverage slows down genetic diversity of SARS-CoV-2

Dear Editor,

A third dose of COVID-19 vaccine has been proved to be necessary to boost antibody level after vaccination for six months [1]. However, the emerging variants of concern (VOC) such as Delta and Omicron tend to weaken the protection of current vaccines [2]. With the observed waning effectiveness of booster shots [3], whether to get additional doses of vaccine in the future remains

an open question. A previous study on influenza showed inadequate vaccination might potentially promote genetic diversity of H5N1 virus [4], but the effect of vaccination on SARS-CoV-2 still remains unknown.

In this study, we downloaded nucleotide sequences of spike protein of SARS-CoV-2 from GISAID [5] (<https://www.gisaid.org>) and classified them by month from Mar. 2020 to Feb. 2022. Daily vaccination rates were collected from Our World in Data [6]. Increases in genetic diversity of SARS-CoV-2 suggested more mutations, which resulted in more potential VOC and infections [7]. Shannon entropy was used to calculate genetic diversity of viruses

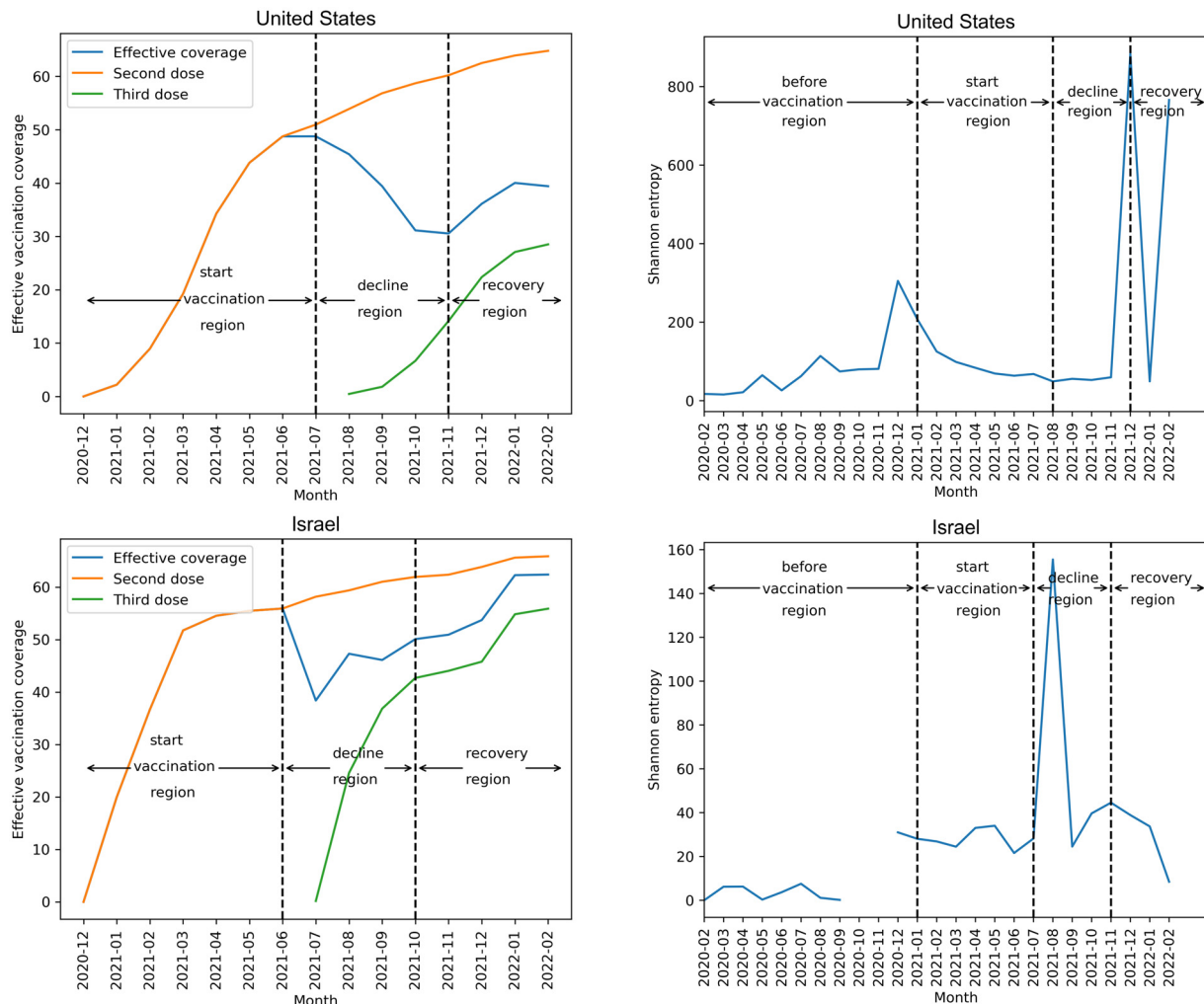


Fig. 1. Tendency of regions with effective vaccine coverage and Shannon entropy in United States, Israel, Poland and Switzerland.

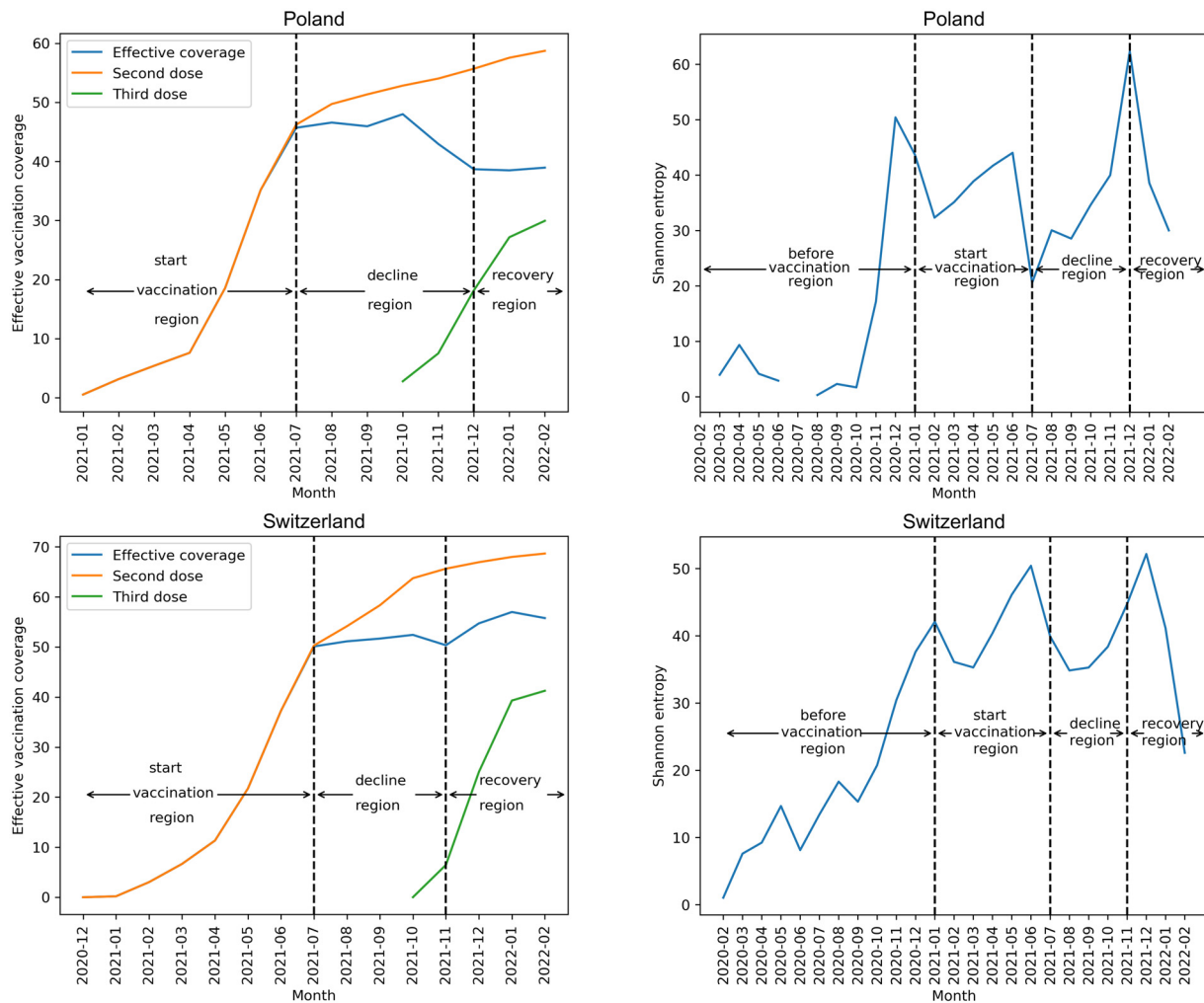


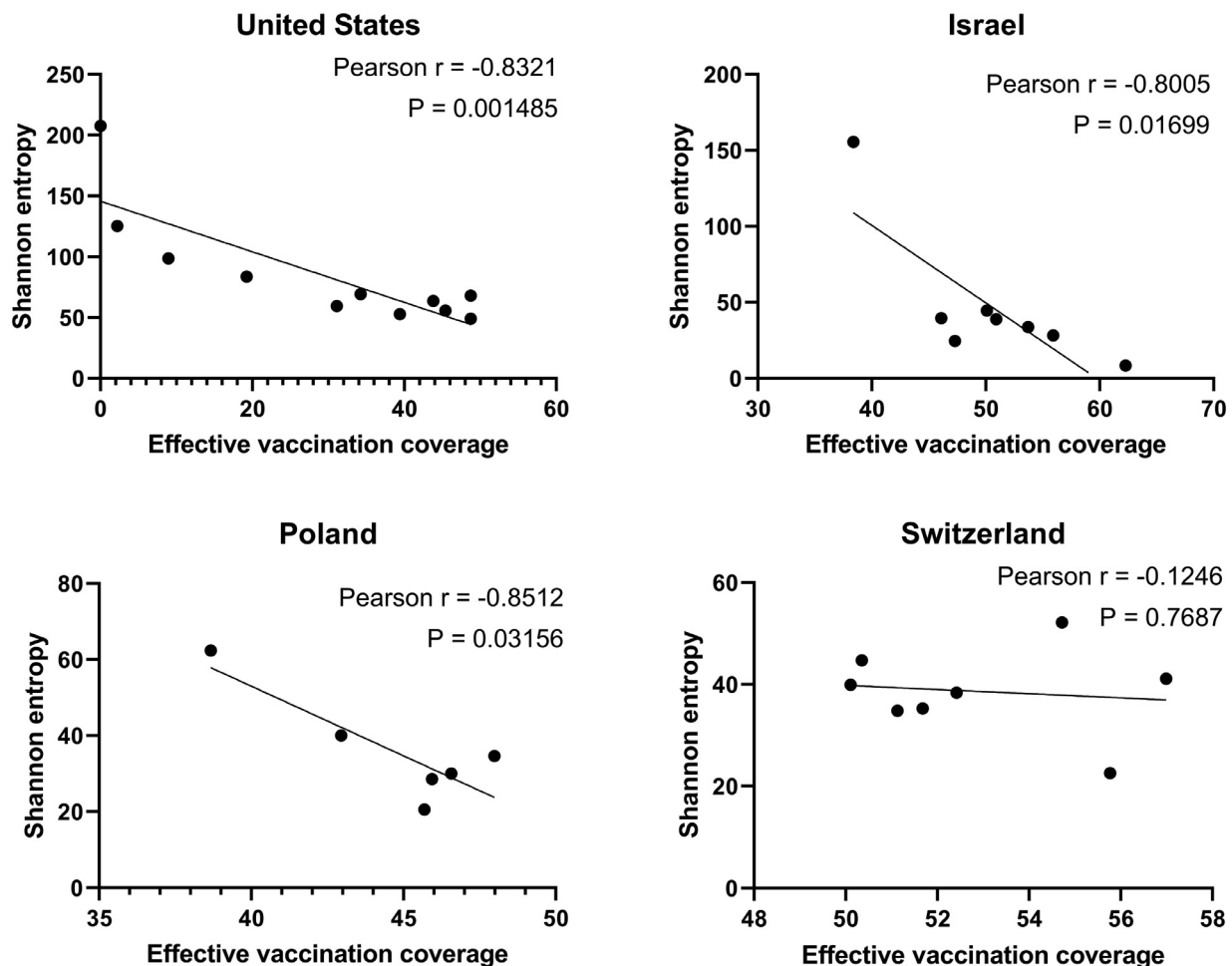
Fig. 1. Continued

on each site or the whole sequence [8]. Considering the time interval between the second and third doses and immunity period of current vaccine, an effective vaccination coverage (EVC) was defined by summation of daily vaccination rates of the second and third doses on the last day of per month minus that of the second dose six months before. Time periods of vaccination were divided into different regions by changes in the trends of EVC. To study relationship between genetic diversity of SARS-CoV-2 and vaccination, correlation analysis of Shannon entropy and EVC were performed.

Three representative countries (United States, Israel and Poland) with EVC evidently declined were selected (Fig. 1). We caught a significant negative correlation between EVC from Dec. 2020 to Oct. 2021 and Shannon entropy with one month delayed above period in United States with Pearson  $r < -0.8$  (Fig. 2). Though significant correlation was not observed in the other two countries, the Shannon entropy oscillated in limited ranges and never exceeded the last highest point during the start vaccination region. A sharp decline of EVC appeared in United States, leading to a violent fluctuation of Shannon entropy during the decline region on Nov. and Dec. 2021, it is the time the Omicron variant emerged. Similar trend was observed in Israel after Jun. 2021 but with one month delayed. In Poland, a sharp rise of Shannon entropy was observed in the same time when EVC fell into sluggish growth and then decreased during the decline region. Both above processes in Israel and Poland had high negative correlation with

Pearson  $r$  value  $< -0.8$ . With rapid follow-up of booster shots in recovery region and EVC exceeding 50 percent again, the Shannon entropy was significantly suppressed in Israel. The Shannon entropy evidently declined in recovery region in both United States and Poland, while EVC stabilized at about 40 percent. Shannon entropy rose again immediately in United States in Feb. 2022 with EVC still below 50 percent, however, more data are needed to observe. We supposed that EVC might be not less than 50 percent to have an effect on the genetic diversity of SARS-CoV-2. And another representative country Switzerland was selected for validation, which had EVC stabilized around 50 percent. Though second dose coverage and EVC diverged from Jul. 2021, Shannon entropy only oscillated in a limited range in decline region in Switzerland and finally declined in recovery region with coverage over 55 percent.

Based on above analysis, we believe continuous EVC over 50 percent may effectively suppress genetic diversity of SARS-CoV-2. Weakening effectiveness of second dose vaccination without booster shot in time may cause a more serious rebound or fluctuation of genetic diversity. It is now generally believed that SARS-CoV-2 might become an endemic virus [9] and evolution of SARS-CoV-2 will continue [10], annual vaccination should be necessary referring to strategy on seasonal influenza. With the potential trend of enhanced immune escape of emerging SARS-CoV-2 variants and weakening of current vaccine [11], our study suggested next booster shot should be carried out before evident weakening



**Fig. 2.** Correlation analysis of United States by effective vaccination coverage from Dec. 2020 to Oct. 2021 with Shannon entropy one month delayed, Israel from Jun. 2021 to Oct. 2021 with one month delayed, Poland from Jul. 2021 to Dec. 2021 and Switzerland as control from Jul. 2021 to Feb. 2022 in the same period.

of the third dose and strategies of vaccination to quickly reach the rate of EVC over 50 percent should be seriously considered.

### Declaration of Competing Interest

None.

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